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Appearance and morphologic features of laryngeal tuberculosis using laryngoscopy

A retrospective cross-sectional study

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Abstract

Laryngeal tuberculosis (LTB) is highly contagious and can cause permanent laryngeal damage. Therefore, correctly identifying laryngoscopic LTB lesion locations, sizes, and morphologic features are essential for LTB diagnoses. This study aimed to explore the appearance and morphologic features of LTB and correlated these features with clinical symptoms.

We retrospectively analysed 39 LTB patients in our hospital between January 2013 and December 2019. Medical records, including clinical presentation, lesion appearance (locations, sizes, and morphology), complementary examination results, and histopathologic features were summarized and analysed.

In this patient cohort, dysphonia and sore throat were the two most common clinical symptoms. In LTB patients with extensive lesions, ulcerative lesions were most common, and the proportion of cases with concurrent pulmonary tuberculosis (86.4%, $P = .033$) infection was higher, as were the positive rates of sputum smears (72.7%, $P = .011$) and cultures (86.4%, $P = .002$) than patients without concurrent pulmonary TB and with more localized and exophytic lesions. The histopathologic features of LTB-related ulcerative lesions included fewer granulomas and more areas with caseous necrosis. These lesions were more likely to have acid-fast bacilli detected with a Ziehl–Neelsen stain than exophytic lesions that rarely showed detectable bacilli.

A complete knowledge regarding the visual and morphologic features of LTB on laryngoscopy is needed for the early detection and diagnosis of LTB. Our study revealed the lesion sites, sizes, and morphologic features of LTB. These parameters were also correlated with patient clinical symptoms. Future studies are needed to support and expand the results of this retrospective study.

Abbreviations: ENT = Ear nose and throat, IGRAs = interferon-gamma release assays, LTB = laryngeal tuberculosis, PCR = polymerase chain reaction, PPD = purified protein derivative, TB = tuberculosis, TST = tuberculin skin tests.

Keywords: laryngeal tuberculosis, larynx, morphology, tuberculosis

1. Introduction

According to the World Health Organization, tuberculosis (TB) sickened 10.0 million and killed 1.2 million HIV-negative people worldwide in 2018.[1] Currently, TB remains the leading cause of death by a single infectious agent.[1] Although TB infections have stabilised in recent years, TB remains a major public health challenge with the AIDS epidemic and the emergence of drug-resistant TB organisms, especially in developing countries with relatively poor medical conditions.[1,2]

Laryngeal tuberculosis (LTB) is the most common granulomatous disease of the larynx. It also has the highest incidence of all TB infections, including ear, nose, and throat TB.[3,4] Since LTB represents an extrapulmonary form of TB, it accounts for only ~1% of total TB incidences.[5–7] However, LTB and pulmonary TB infections are often concurrent. In these situations, laryngeal examinations are not usually performed, and only pulmonary TB infections are diagnosed, missing concurrent infections. Accordingly, the incidence of LTB infections is likely seriously underestimated.[8,9]

Laryngeal structures are extensively damaged in LTB infections. This damage can result in permanent laryngeal dysfunction due to scars and tissue defects if therapies are not performed in a reasonable amount of time.[10,11] However, at present, the detection and diagnosis of extrapulmonary LTB infections, whether alone or concurrent with pulmonary TB infections are poor. Several reports have shown that the time from LTB infection to disease diagnoses can be months or even years.[12,13]

Similar to pulmonary TB, LTB is highly contagious; and therefore, early diagnoses are imperative to plan both therapeutic and public health strategies. LTB infections often have no systemic symptoms; however, prominent laryngeal symptoms can occur, which means that initial TB diagnoses are frequently

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made in otorhinolaryngology departments. Since laryngeal symptoms are not pathognomonic for LTB infections, it is important to identify the locations, sizes, and morphologic features of LTB using laryngoscopy. If an LTB infection is suspected, additional TB-related testing can be pursued, leading to a confirmatory diagnosis. However, LTB infections have been shown to have various morphologic characteristics.[7,14–16] In this clinical study, we found that patients with LTB infections had characteristic appearances and morphologic features associated with both clinical symptoms and histopathologic features.

Therefore, in this study, to further recognize and better diagnose LTB infections, we retrospectively analysed the clinical symptoms, visual and morphologic laryngoscopic features, histopathologic characteristics, and complementary clinical examinations of patients with LTB.

2. Materials and methods

2.1. Patients

This retrospective cross-sectional study was approved by the Ethics Committee of the First Affiliated Hospital of China Medical University, Shenyang, China. The collection of patient data was exempt from needing patient informed consent since personal information was not accessed. Patients diagnosed with LTB infection at our hospital between January 2013 and December 2019 were included in the study. Demographic data, including age, gender, comorbidities, and clinical presentations, including systemic and local laryngeal symptoms, were accessed. LTB features, including lesion sites, the extent of involvement, and morphologic features, were assessed with a fibreoptic laryngoscope (ENF-T3, Olympus, Tokyo, Japan). The diagnostic criteria for LTB infections included at least one of the following, in addition to finding lesions in the larynx, chronic granulomatous inflammation with caseous necrosis, acid-fast positive staining on histopathologic tissue sections, and acid-fast positive bacilli on sputum smears or in cultures. Exclusion criteria included a lack of complete information in the medical records. All confirmed patients were transferred to The TB Hospital (Shenyang Chest Hospital) for standard anti-TB chemotherapy.

2.2. Complementary examinations

All patients underwent thoracic imaging, TB skin tests (TSTs), and sputum tests. Thoracic radiographs (pulmonary computed tomography, if necessary) were performed to determine the presence of concomitant pulmonary TB infections. The purified protein derivative (PPD) skin test was considered positive if the skin in duration was >5 mm in diameter. Acid-fast bacilli were detected on sputum smears and tissue sections using the Ziehl–Neelsen staining technique.[17] A polymerase chain reaction (PCR) was used to detect Mycobacterium TB complex DNA in biopsy tissues. The T-SPOT test was performed on peripheral blood samples.

2.3. Statistical analyses

The Statistical Package for the Social Sciences (SPSS 22.0, IBM SPSS Corp, Armonk, NY) was used to analyse the data. The quantitative variables were presented as the mean ± standard deviation (SD) and the median. The *t* test and Mann–Whitney *U* test were used to compare the quantitative variables. The categorical variables were presented as n (%), and the associations between categorical variables were analysed using the chi-square and Fisher's exact tests. A *P*-value of $<.05$ indicated statistical significance.

3. Results

3.1. Patient demographics

A total of 43 patients were diagnosed with LTB. Four (9.3%) patients were excluded due to incomplete medical records, leaving 39 patients with LTB infections included in this study. The male-to-female ratio was 2.6:1. The age ranged from 20 to 89 years of age; the average age was 47.5 ± 15.8 years of age, and the median age was 48 years of age. The interval between the onset of clinical symptoms and the final diagnosis was 1 to 25 months (median, 6.9 months). Other details are shown in Table 1.

3.2. Morphologic categories of the LTB lesions

According to relevant research[14–16] and our clinical observations, we summarized three morphologic categories for LTB lesions. The first category is represented by nonspecific exudative inflammatory lesions characterized by tissue oedema or hyperaemic swelling associated with smooth surfaces or covered with small amounts of exudate (Fig. 1A). The second category involves ulcerative lesions characterized primarily by mucosal and submucosal ulcers that sometimes involve the

Table 1

Clinical data and complementary examination results of 39 patients with laryngeal tuberculosis.

Characteristics		Number (%)
Gender	Male	28
	Female	11
Medical history and comorbidities	History of pulmonary TB	8 (20.5)
	Diabetes	5 (12.8)
	Immunosuppressive states (infection of HIV)	0 (0)
	Comorbidity with malignancy	0 (0)
Local symptoms	Dysphonia including hoarseness and aphonia	33 (84.6)
	Sore throat including odynophagia	26 (66.7)
	Dyspnea	4 (10.3)
	Dysphagia	7 (17.9)
	Cough with sputum	20 (51.3)
	Irritating dry cough	7 (17.9)
Systemic symptoms	Weight loss	16 (41)
	Fever	9 (23.1)
Lesion extent (number of the affected sites)	Localized lesions (≤2)	17 (43.6)
	Extensive lesions (≥3)	22 (56.4)
Pulmonary imaging examination	Suggests concomitant pulmonary TB	28 (71.8)
PPD test	Positive	29 (74.4)
Sputum smear	Positive	21 (53.8)
Sputum culture	Positive	25 (64.1)
Histopathological biopsy (N = 26)	Ziehl–Neelsen staining (+)	4 (15.4)
	PCR analysis of mycobacterial DNA (+)	20 (76.9)
Interferon-gamma release assays (N = 6)	T-SPOT.*TB* (+)	5 (83.3)

N = performed number, PPD = purified protein derivative, TB = tuberculosis.

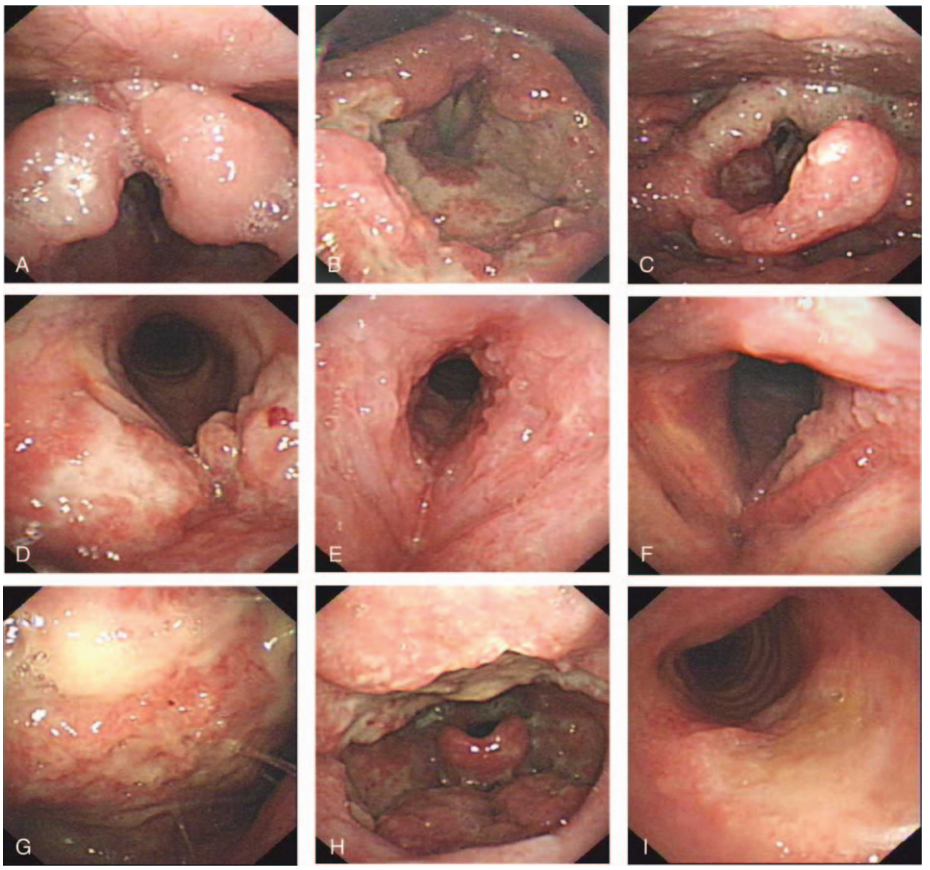

Figure 1. Morphologic category of LTB lesions. The representative pictures of LTB obtained by fiberoptic laryngoscopy from different patients in their first presentation: (A) Nonspecific inflammatory lesion: arytenoid region showed pale edema with smooth surface. (B) Ulcerative lesion: extensive ulcers with insect bite-like appearance located in epiglottis, bilateral false vocal cords, and aryepiglottic fold. (C) Erosion of half the epiglottis caused by severe ulcers. (D) Exophytic lesion: granulomatous hyperplasia and mass located in false vocal folds. (E) Fibrosis and scar contracture of glottis and subglottis. (F) Exophytic lesion was confined to the left vocal cord. (G) Tuberculosis of nasopharynx. (H) Tuberculosis of oropharynx. (I) Tuberculosis of main trachea.

perichondrium and cartilage of deep structures, especially those of the epiglottic and arytenoid cartilage. The ulcers have a main insect bite-like appearance accompanied by large amounts of grey exudation, and the ulcer bases are composed primarily of granulation tissue (Fig. 1B). Severe ulcerative erosions sometime lead to tissue defects (Fig. 1C). The third category is represented by exophytic lesions that are essentially tuberculous granulomas manifesting as hyperplastic masses with rough surfaces (Fig. 1D). Hyperplastic fibrous tissues that infiltrate lesions in advanced LTB infection stages could result in scar contractures (Fig. 1E).

To describe the lesion sizes more accurately, we divided the larynx into seven anatomic sites: vocal cords, false vocal cords, the epiglottis, arytenoid region, aryepiglottic fold, inter-arytenoid region, and subglottis. We defined LTB lesion involvement in fewer than three anatomic sites as localised lesions (Fig. 1F). Extensive lesions were defined as those having three or more anatomic sites affected (Fig. 1B).

3.3. Clinical symptoms of LTB infection and location of LTB lesions

Dysphonia and sore throat were the two most common clinical symptoms (Table 1). These two symptoms co-existed in 14 patients (35.9%). A productive cough with sputum was present in 20 patients (51.3%), and they were all accompanied by pulmonary TB. The main systemic symptoms were weight loss (weight loss of over 5%) and fever (37.5–39.5°C). See Table 1 for details.

In this study, lesions were restricted to a single anatomic site of larynx, in 8 patients, including four patients with vocal cord, three with epiglottal, and one with false vocal cord lesions. Among the patients with multiple sites involved (≥3 sites), lesions extended beyond the larynx to the nasopharynx in 2 cases, to the oropharynx in three cases, and the main trachea in two cases, as shown in Figure 1G–I.

3.4. Morphologic features of and sites with LTB lesions

Each anatomic site had one of the three morphologic features presented above (Fig. 2A–I). The morphologic features of the lesions at each anatomic site in this series, is shown in Table 2. The vocal cord was most frequently involved (33/39 cases, 84.6%), and the main lesion morphologic type was exophytic (19/33 sites, 60.6%). The epiglottis was the second most common site (25/39 cases, 64.1%), and ulcerative lesions were most common (12/47 sites, 25.5%). The lingual surface of the epiglottis and the arytenoid region were the main sites of nonspecific inflammation. In terms of the total sites involved, exophytic lesions were the main lesion types (55/133 sites, 41.4%); details are shown in Table 2.

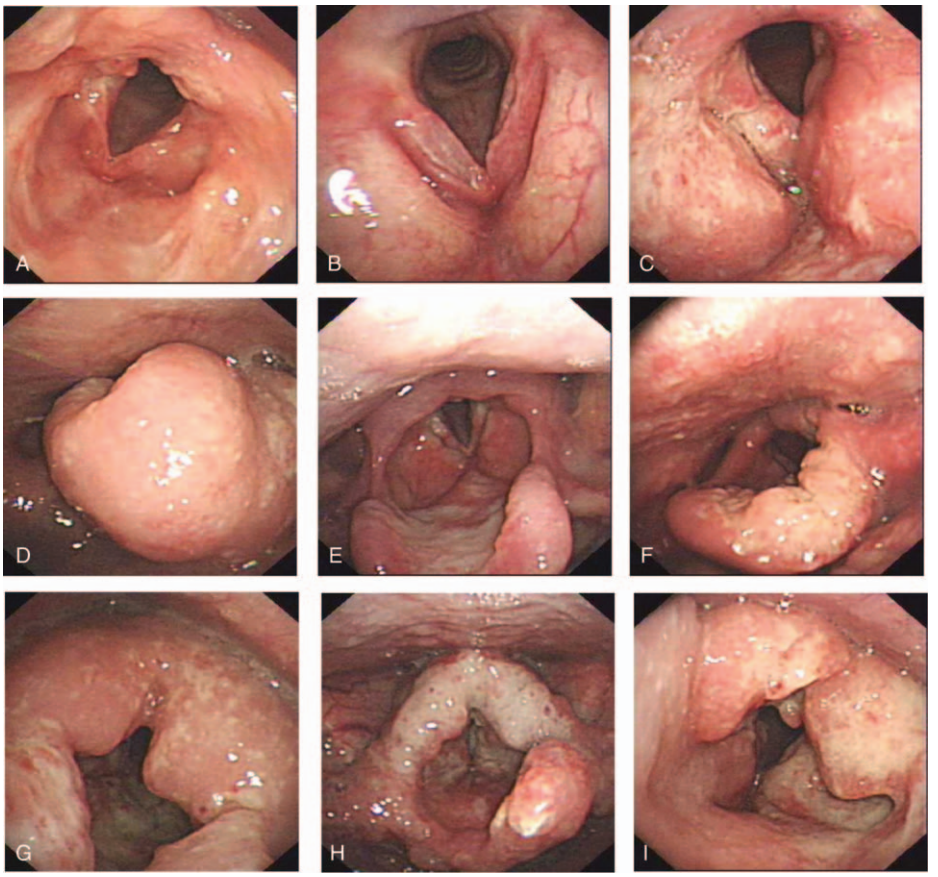

Figure 2. Morphologic features of and sites with LTB lesions. The representative pictures obtained from different patients in their first presentation: (A–C) Nonspecific inflammatory (A), ulcerative (B), and exophytic (C) lesions of vocal cords. (D–F) Nonspecific inflammatory (D), ulcerative (E), and exophytic (F) lesions of epiglottis. (G–I) Nonspecific inflammatory (G), ulcerative (H), and exophytic (I) lesions of arytenoid region.

In 39 patients, a total of 133 anatomic sites were affected (Table 2), including 107 sites in 22 patients with extensive lesions (≥3 sites), and 26 sites in 17 patients with localised lesions (≤2 sites). Ulcerative lesions were most common in patients with extensive lesions (43 sites, 40.2%). Conversely, exophytic lesions were most common in patients with localised lesions (18 sites, 69.2%). A statistical difference between these two sites was also found ($P = .004$).

Although only one morphologic type was usually dominant in an individual LTB patient, some patients had two or three lesion types present simultaneously at the same or different sites within the larynx. Figure 3A shows a left vocal cord with an ulcerative lesion, while the right vocal cord shows an exophytic lesion with additional ulcerative lesions around it; the exophytic lesion likely transformed from an ulcerative lesion. Figure 3B and C shows an exophytic tuberculous granuloma and severely damaged and scarred epiglottis, respectively, in the same patient. It is speculated that an ulcerative lesion was predominant in the early stages of LTB infection in this patient causing epiglottal cartilage necrosis and resultant defects. In the later stages, false vocal folds appeared as hyperplastic granulomas likely arising from an ulcerative lesion.

3.5. Correlations with clinical examinations

Among the LTB patients with extensive lesions, the proportion of those with pulmonary TB infection (86.4%, $P = .033$) was higher, as were the rates of positive sputum smears (72.7%, $P = .011$) and cultures (86.4%, $P = .002$; however, these findings were not associated with the PPD test results or disease durations ($P > .05$). Furthermore, concomitant pulmonary TB infections were not associated with the differing laryngeal lesion locations ($P > .05$).

Table 2

Tuberculous lesion morphologies and sites involved in the larynx of 39 LTB patients.

Laryngoscopic findings	Vocal cords	False vocal cords	Arytenoid region	Aryepiglottic fold	Interarytenoid region	Epiglottis	Subglottis
Nonspecific inflammatory lesion	4	2	10	4	2	9 (lingual surface)	0
Ulcerative lesion	10	8	6	6	4	12 (laryngeal surface)	1
Exophytic lesion	19	12	7	7	5	4	1
Total	33 (84.6%)	22 (56.4%)	23 (59%)	17 (43.6%)	11 (28.2%)	25 (64.1%)	2 (5.1%)

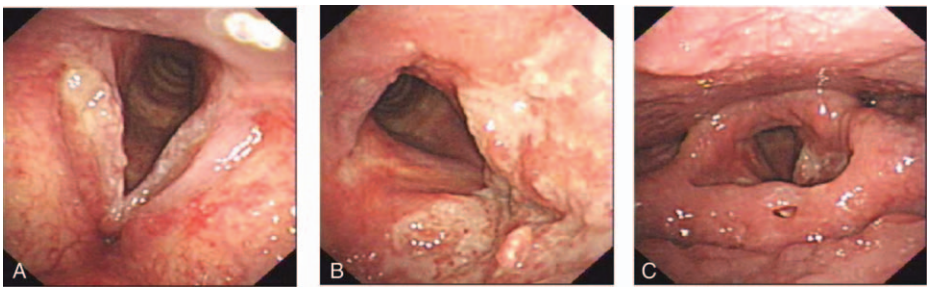

Figure 3. Different morphologies of LTB can exist simultaneously and transform each other. (A) This image obtained from an untreated patient. The left vocal cord showed ulcerative lesion, while the right vocal cord formed an exophytic lesion. (B) and (C) were images from the same patient under different fields of view during the first fiberoptic laryngoscopy. (B) Exophytic tuberculous granuloma of the false vocal cords was formed. (C) Severe defect and scar formation of epiglottis.

In addition, among the 11 patients without imaging evidence of pulmonary TB infection, localised exophytic laryngeal lesions ($\leq$2 sites) were most common (72.7%, $P = .033$) compared with those with concurrent pulmonary TB infections. However, relatively rare positive sputum smear (0%) or culture (9.1%) results ($P = .000$) were seen in these patients. Accordingly, histopathologic biopsies were often needed to confirm the final diagnoses.

3.6. Histopathologic features

Twenty-six patients had lesion biopsies performed. The typical histopathologic feature observed was epithelioid cell granuloma formation with varying degrees of caseous necrosis, surrounded by lymphocytes and Langhans giant cells (Fig. 4A and B). Among the biopsies, eight cases showed ulcerative lesions characterized primarily by caseous necrosis with decreased granuloma formation (Fig. 4C). Conversely, the histopathologic characteristics of

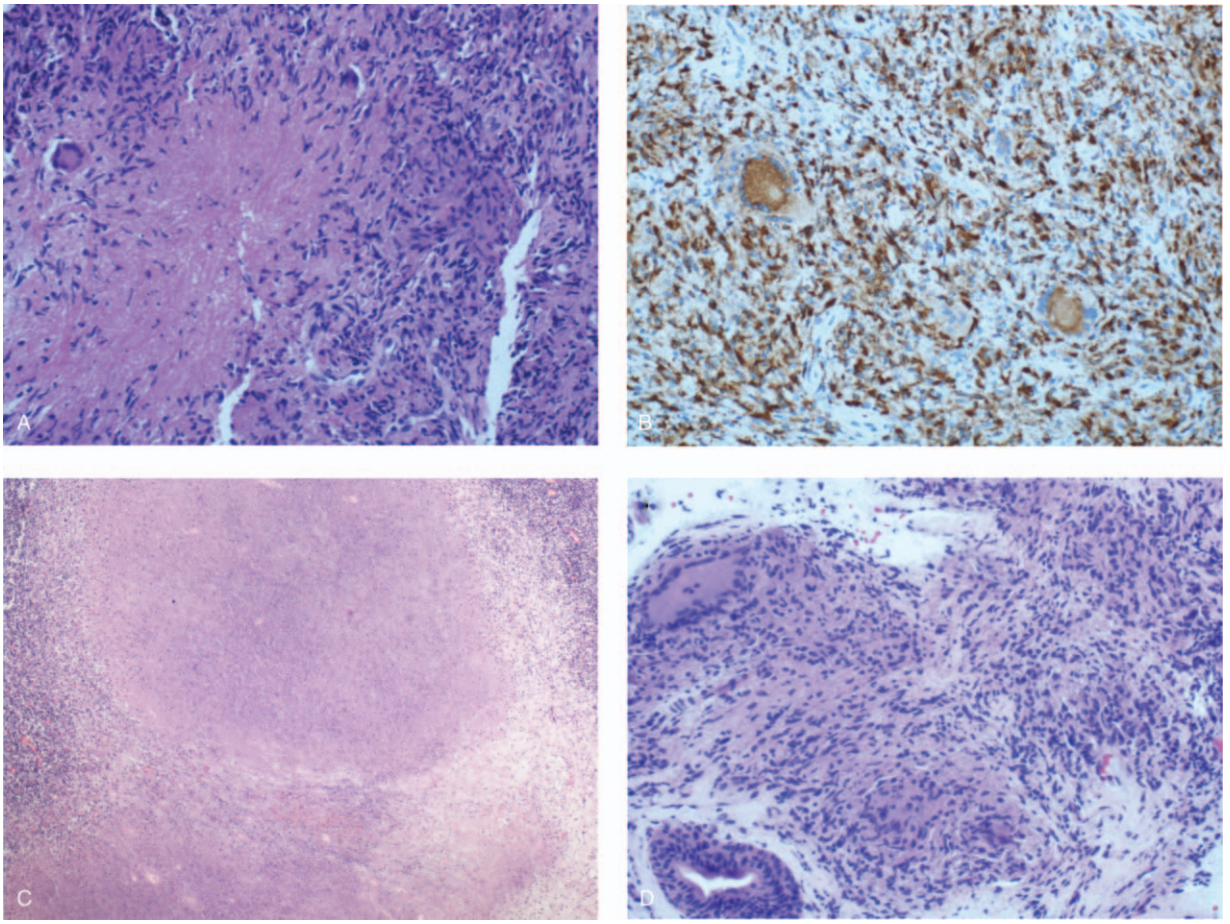

Figure 4. Histopathologic feature of LTB (A) The typical histopathologic feature observed was epithelioid cell granuloma formation with varying degrees of caseous necrosis, surrounded by lymphocytes, and Langhans giant cells (H&E, ×100). (B) Epithelioid cells and Langhans giant cells were positive for CD68 (immunohistochemical stain, ×400). (C) There was a large area of caseous necrosis in a biopsy from ulcerative lesions (H&E, ×40). (D) Epithelioid granuloma formation with no obvious caseous necrosis was showed in a exophytic lesion biopsy (H&E, ×100).

exophytic lesions (18 patients) were mainly epithelioid granulomas associated with focal areas of caseous necrosis or no obvious necrosis (Fig. 4D). The positivity rate of the histopathologic sections using Ziehl–Neelsen staining was 15.4% (4 cases), and, in all four cases, the bacilli were associated with ulcerative lesions. When these findings were compared with those of exophytic lesions, a statistical difference was found ($P = .005$). Mycobacterial TB DNA was found in 21 specimens (80.8%) using PCR analyses. The detection rates of Mycobacterium TB DNA were not significantly different between the ulcerative and exophytic lesion types ($P > .05$).

4. Discussion

Although China has a low incidence of LTB infections, the population of TB infections is substantial. In 2018, the number of new TB cases in China was 0.86 million, which accounted for 8.6% of new global TB cases, ranking China as second in the world for this debilitating disease.[1] Therefore, as a regional diagnostics and treatment center, our hospital receives LTB patients more frequently than other hospitals. The pulmonary and systemic symptoms of LTB infections are sometimes so negligible that physicians might not be aware that this disease could be present. Consequently, otorhinolaryngologists should have a complete understanding of the visual and morphologic features on laryngoscopy in patients with LTB infection. The related clinical symptoms should also be known so that misdiagnoses and missed diagnoses can be reduced.

Most patients with LTB infections were between 40 and 50 years of age at the onset of this study. There were more male than female patients, and the gender ratio was consistent with most other studies.[14,15,18–21] In an earlier case series, patients infected with LTB were mostly 20 to 30 years of age.[3,22] Recent studies have reported that patients were between 50 and 60 years of age, especially in developed countries.[15,20] Therefore, the patient ages in our study fell between those of these other studies. No HIV-infected patients were identified in our study, likely because HIV is not at epidemic proportions in China.[1,23] Similar to the study by Magee et al, no significant correlation was found between the occurrence of diabetes mellitus and LTB infection.[24]

The main clinical symptom of LTB infection was dysphonia, which was consistent this study's finding that LTB lesions were primarily found in the vocal cords. This result was similar to the results of most other LTB studies.[10,15,16,20–22,25] We also observed a higher frequency of sore throats in our patient cohort. Odynophagia was more excruciating in patients with epiglottal and arytenoid regional lesions than in those without lesions in these areas. The reason for increase pain in these two areas is because they are involved in active swallowing. Dysphagia occurs in patients with severe odynophagia, which can lead to eating disorders and weight loss.[8] Patients with varying degrees of dyspnea were mostly due to exophytic lesions or scar strictures in the glottis or subglottis, causing airway obstructions.[3] The percentage of LTB patients with productive coughs, sputum, and concomitant pulmonary TB infections was 51.3% (20 cases), indicating that a significant portion of patients lacked obvious sputum production. These results suggested that the LTB is not only transmitted through sputum but could also be spread through blood or lymph tissues.[8,14,15,26] Moreover, the proportion of LTB patients with systemic symptoms was lower than those with local symptoms, which is supported by many recent case reports.[3,9,20,22,27] Changes in symptoms and the types and forms of transmission could be related to the long-term and irregular use of anti-TB drugs or the emergence of drug-resistant TB bacilli.[22,26,28]

In this study, we found that most patients had LTB lesions in the vocal cords, as has been frequently reported.[8,10,15,16,20–22,25,26] The vocal cords are primary sites of infection because the glottis represents the entrance to the respiratory tract, and is thus, the first area to be exposed to the bacilli whether expectorated from the lungs or inhaled from air droplets.[3] Furthermore, vocal cord mucosal injuries caused by chronic coughs or excessive vocalizing also increases the chance of bacterial invasion.[9]

When examining the locations of the three different morphologic LTB lesion types, we found that all morphologic types could be found in any part of the larynx. Exophytic lesions were the most common in this study, a finding that was supported by previous study results.[8,15,20,22,26,29] In agreement with a study by Reis et al, the laryngeal surface of the epiglottis was more likely to have ulcerative lesions compared with other locations, and the lesions were erosive in this study.[8] The gross morphologic features of LTB lesions were shown to be closely related to those of the histopathologic tissue sections from different anatomic sites in the larynx.[30] Because the epiglottis has less submucosal tissue than that other laryngeal structures, the mucosa has a direct and firm attachment to cartilage. Therefore, during LTB infection, ulcerative lesions are more likely to occur in this location. In contrast, hyperemia and swelling often occur in the areas where the submucosal tissues are more loosely attached, such as at the lingual surface of the epiglottis and arytenoid region, as shown in this study.

The various morphologic LTB types can exist at the same or different anatomic sites simultaneously and can transform from one type to another at different stages of LTB development. In the early stages of LTB infection, when allergic reactions are prominent, exudative inflammation is mostly present with tissue oedema and/or hyperemic swelling. When high numbers of or extremely virulent TB bacilli are present, tissue necrosis and ulceration start to form.[20] When physical conditions improve or the number and/or virulence of the TB bacilli decrease, hyperplastic TB granulomas form over the ulcerative lesions.

We found that patients with extensive LTB lesions (≥3 sites) were more likely to have ulcerative lesions and also tended to have pulmonary TB infections. A higher number of positive sputum smears and cultures were found in these patients, similar to the conclusions of a few other studies.[8,15] In contrast, LTB infections without concurrent pulmonary TB infections often present as localised, exophytic lesions in the larynx, and TB bacilli are challenging to identify in sputum samples,[14,22] causing a diagnostic dilemma. Some other studies have reported that even when positive sputum test results are present, it is difficult to discern if the bacilli came from the larynx or the lungs in patients with both LTB and pulmonary TB infections.[3,8]

A biopsy is usually performed to assist in making an LTB diagnosis and to rule out other benign and malignant tumors. Although no coexisting tumors were identified in this study, there have been many reports showing the coexistence of LTB infections and cancers, which suggest that one disease could facilitate the other.[29,31,32] Biopsies were often selected at exophytic or ulcerative lesions. We found that exophytic lesions usually consisted of epithelioid granulomas, accompanied by decreased areas of caseous necrosis. In contrast, ulcerative lesions usually had fewer granulomas with more areas of caseous

necrosis, and the acid-fast bacilli were more susceptible to positive staining using the Ziehl–Neelsen stain. Overall, however, the positive rate of Ziehl–Neelsen staining in tissue sections is often very low as reported here and in other studies.[8,9,27] The PCR detection of Mycobacterium TB DNA has been shown to provide higher sensitivities and specificities for TB diagnoses.[26,28,33] However, diagnosing epithelioid cell granulomas with caseous necrosis on histopathologic tissue sections can be used as a clinical diagnostic standard to initiate anti-TB therapy.[3,15,16,26] As an interferon-gamma release assay (IGRA), the T-SPOT assay has been demonstrated to be more sensitive and specific compared with that of the PPD test for LTB diagnoses.[34,35] However, IGRAs are expensive to run, and therefore, cannot replace the tuberculin skin test (TST) in the regions with middle-to-high TB incidences.[2]

Anti-TB therapy can often cure LTB infections.[15] Significant improvement usually appears within weeks, including an improvement in symptoms and laryngeal appearances, which could return to normal within several months. However, if large defects or scar adhesion are present in the larynx, permanent functional laryngeal damage could occur. In the event of severe dyspnoea caused by laryngeal obstruction, surgical intervention can be performed. An anti-TB chemotherapy treatment period of at least 6 months that can be extended to 12 months when accompanied by pulmonary TB is common and includes 2 months of intensive treatments (rifampin, isoniazid, pyrazinamide, and ethambutol) followed by a maintenance treatment of two or three drugs.[3,8,9,16] Although the efficacy of anti-TB treatment is satisfactory, in clinical practice, we found that if patients received inadequate or irregular anti-TB treatment, LTB often recurred, and its morphology often showed exophytic lesions. The reason may be that the irregular use of anti-TB drugs led to the dormancy or variation of Mycobacterium TB, which weakened its pathogenic ability, resulting in morphological changes of LTB.[1,22,23,36]

There were a couple limitations to this study. First, this was a retrospective study that received information from outpatient medical records; and therefore, some TB-related factors could not be examined. Second, patient numbers were small, and future studies looking using a larger number of patients should be performed to support our results.

5. Conclusions

In this study, we showed that laryngeal morphologic changes associated with LTB infections had specific characteristics and that some were related to the clinical presentations, complementary examinations, and histopathologic features. An adequate understanding of the visual and morphologic features of LTB infection on laryngoscopy is crucial for the early detection and accurate diagnosis of this challenging infectious disease.

Author contributions

Conceptualization: Xuejun Jiang.
Data curation: Jian Zang, Xuejun Jiang.
Methodology: Jian Zang, Ying Tian.
Writing – original draft: Jian Zang, Ying Tian.
Writing – review & editing: Xuejun Jiang, Xu-yong Lin.

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